

REMARKS/ARGUMENTS

The independent claims are being amended to require that the ratio of the amount of bile acid + additive to the active macromolecular principle is at least 3:1 based on page 8 line 12 of the description. Also to correct a typing error, claim 31 is being reformulated as a composition claim. The counterpart method claim is claim 32.

The comments that follow are based on those provided informally to the Examiner before the interview of April 8, 2008. A statement of the substance of that interview was provided in the Interview Statement mailed April 21, 2008. The comments have been modified to (i) include the Applicant's summary of the contribution the present invention makes over his own US 5,853,748; (ii) highlight why the advantageous effect of the additives used in the present invention is unexpected; and (iii) expand the comments on the prior art document Desai, which according to counsel's understanding the examiners consider to be the most relevant.

Before considering the objections raised in the Office Action, it may be helpful to summarize the contribution that the present invention makes over the prior art, and in particular the prior art document US 5,853,748 (hereafter New '748).

It seems that the Examiner may have failed to appreciate that, although (New '748) and the present invention seek to achieve the same objective (improved efficacy of bile salts) they have focused on different hurdles, and have overcome them in very different ways. In New '748, the observation has been made that bile salts have lower toxicity at high pH, thus, a formulation that raises the pH above that found in the gut may be advantageous because it could enable larger amounts of bile salt to be administered. The present application, in contrast, notes that non-conjugated bile salts are poorly soluble at the pH levels that are normally found in the gut (4 – 7), and teaches a method of making these bile salts more readily available (and more efficacious) without altering the pH outside the normal range. The examples in the present application demonstrate that solubility is improved in simulated intestinal fluids at pH levels between 5 and 6.5.

It should be noted that, as described in the examples, the pH of the formulation before drying is adjusted to pH 7.5 or less, so when the powder is mixed with intestinal contents at a pH lower than 7, there is no way in which the pH could rise above 7.5, let alone reach 8 as in New '748. [It should also be borne in mind that, just because a molecule has a pKa at a certain value,

this does not mean it will have a strong buffering capacity at that value, and indeed, the further away the pH is from that value, the less buffering capacity it will have.]

The Office Action

Firstly, the applicant respectfully disagrees with the Examiner's assertion that the feature of claim 1 "wherein the composition, when introduced into the intestine, does not raise the pH of the intestinal fluid above pH 7.5" should be given no patentable weight. The Examiner quotes from the MPEP 2106 and states: "language that suggests or makes optional or does not limit a claim to a particular structure does not limit the scope of a claim or claim limitation...". The applicant simply cannot accept the suggestion that the above-mentioned feature "suggests or makes optional" a limitation to claim 1. The feature is essential to claim 1, and clearly excludes any composition that would raise the intestinal fluid pH above 7.5.

To illustrate the effect of having this feature, consider a composition containing the three components (a), (b) and (c) as defined in claim 1, with the requisite 1 wt% or more of component (c). The composition could additionally contain an additive that serves to raise the pH of the intestinal fluid (on introduction of the composition to the intestines) to 7.5 or higher. Previously, such a composition may have been covered by claim 1, but now it would not. Thus, the feature should be given patentable weight. Indeed, at page 8 of the Office Action the Examiner appears to have done this.

Inventive Step

As a preliminary point, it should be noted that, as explained in the application as originally filed, the present invention is based on the surprising discovery that the additive defined in claim 1 directly enhances the solubility of a non-conjugated bile acid or salt at pH levels found in the intestine. This enhancement of the bile salt solubility has the effect of improving the (already known) ability of bile salts to act as permeation enhancers. Thus, the present applicant has invented a method of enhancing the absorption of macromolecules, and compositions for doing so. It is believed that nowhere at all in the cited prior art is there even a suggestion that the additive of claim 1 might have this effect of enhancing the solubility of a non-conjugated bile acid or salt. Indeed, as noted in the present application (page 2, lines 11-14) the discovery is entirely surprising.

In particular, the ability of the additives of claim 1 to exert this effect is unexpected because these additives have very poor solubility in water, as is proven by the attached extracts from the Handbook of Pharmaceutical Excipients for butylated hydroxyl anisole (BHA) and propyl gallate (PG). Both are powders at room temperature, and BHA is “practically insoluble” in water while PG has a solubility of 1 in 1000 at 20 °C (see section 10 of the extracts). Moreover, while both are known antioxidants, their known use is preventing rancidity in oils and fats (see section 7 of the extracts). The intestine, on the other hand, is an aqueous environment. Thus, no skilled person would have contemplated using BHA and PG in combination with non-conjugated bile acids and salts in an aqueous environment.

Thus, without the knowledge of the unexpected ability of BHA and PG to enhance the solubility of non-conjugated bile acids and salts in an aqueous environment (i.e. without the benefit of hindsight), a person of skill in the art would have had no motivation to prepare a composition as defined in claim 1, wherein an aromatic alcohol that has very poor solubility in water is combined with a non-conjugated bile acid or salt, with the intention of releasing these components in the aqueous environment of the intestine. This is explained further below.

The Examiner's reasoning

The Examiner notes that New (US 5653987) does not disclose the use of an additive as defined in claim 1. Instead, it uses an inorganic additive, e.g. sodium bicarbonate (see Example 4) in order to raise the gut pH to 7.5-9 following administration.

The Examiner argues that it is obvious to modify the composition of New by replacing sodium bicarbonate with an organic additive as defined in claim 1, in view of the teachings of Makino *et al*, Desai *et al* and Modi *et al*. The Examiner then argues that the knowledge that propyl gallate has a pKa of 8.11 would have motivated a skilled person to replace the sodium bicarbonate with an organic additive as defined in claim 1. Finally, the Examiner asserts that it would be a necessary property of the composition not to raise the pH above 7.5 once it has been introduced into the intestine. These three aspects are dealt with in turn.

The Prior art

First of all, we refer to the Examiner's comment that:

“Applicant seems to be implying that the rejection is based on the New Patent '748 only. However, the rejection is not solely based on the New Patent '748, but a combination of...”

It was not the applicant's intention to imply this, when pointing out that the modification suggested to be obvious by the Examiner is incompatible with the direct teaching of the New '748 patent. Rather, the point made relates to the principle that something disclosed in the prior art cannot simply be modified by selectively replacing a particular feature with a different feature from another piece of prior art, when the feature in said other prior art is disclosed in a different context. This is particularly true when the original "something" is an invention, and even more so when that invention is a pharmaceutical composition, which naturally will be very sensitive to changes in its make-up. Thus, the features in question are inextricably linked to their context, and one cannot simply form a mosaic from different pieces of prior art when formulating an objection of obviousness.

By way of example, if the original "something" was a tennis ball, it would not be obvious to modify the tennis ball by replacing its inner rubbery member with a hard phenolic resin member of the type that billiards balls are made of. Clearly, making such a replacement would lead to a ball which could no longer fulfill its original purpose as a tennis ball. Moreover, one might expect incompatibilities, such as difficulties in attaching the fibrous tennis ball covering to a hard phenolic resin. Thus, it follows that such a replacement would not be obvious, because it would rob the original "something" (i.e. the tennis ball) of its essential properties.

Thus, in the present case, in order to achieve the special effects that New set out to provide in the '748 Patent, it is essential that the composition comprises "an agent having the ability to adjust the pH of the gut to a value of from 7.5 to 9" (see e.g. claim 1 of New). This is the crucial teaching of New (see e.g. col. 2 lines 55-59). Clearly, removing the agent would rob the composition of New of its essential properties. As explained above, the present invention is based on the surprising discovery that the additive defined in claim 1 directly enhances the solubility of a non-conjugated bile acid or salt without taking the pH outside normal limits, thereby improving the ability of the bile salt to act as a permeation enhancer, thereby enhancing the absorption of macromolecules. It is believed that nowhere at all in the cited prior art is there even a suggestion that the additive of claim 1 might have this effect of enhancing the solubility of a non-conjugated bile acid or salt. Thus, there is simply no way that a skilled person would have even contemplated (let alone thought obvious) replacing the crucial ingredient of New's

composition with an additive as defined in claim 1, with an expectation of retaining the essential properties of the composition.

The suggestion that it is obvious to modify a known pharmaceutical composition by replacing its most essential ingredient with a chemically unrelated ingredient, with absolutely no reason to expect the composition's activity to be retained, is not credible. Indeed, if it were the case, a great number of granted patents in the pharmaceutical field would be invalid.

As a further point regarding the prior art-based objection, the Examiner has pieced together no less than four¹ unrelated pieces of prior art (not even counting the CRC Handbook of Chemistry and Physics) in order to "arrive" at a composition of claim 1. Before one even considers what the documents in question disclose, this fact alone suggests the use of hindsight, which is not permitted in the assessment of inventive step.

The three other documents referred to by the Examiner are considered in turn below:

Desai et al: It is suggested that this document teaches that propyl gallate (PG) and butyl hydroxyanisole (BHA) are commonly used in insulin formulations. Desai describes compositions with a lipid component and a polyol component, which together form a microemulsion in the body after oral administration (see e.g. col. 1 lines 5-9 and 60-68). The optional antioxidant mentioned at col. 5 lines 5-18 is specifically present only in the lipid component. Its purpose is to protect unsaturated lipids. Indeed, antioxidants that are oil-soluble are required (col. 5 lines 14-18), so as to ensure that the optional antioxidant remains in the lipid component when the microemulsion is formed, so that it can fulfill its purpose of protecting the lipid from oxidation. Thus, the antioxidant will have an insignificant if any amount interaction with the aqueous part of the environment in the microemulsion. This follows naturally from the fact that BHA and PG have a very low solubility in water (see section 10 of the attached extracts from the Handbook of Pharmaceutical Excipients). Indeed, the use of the antioxidants in Desai

¹ It is noted that 4 references have been asserted as the basis of the Examiner's obviousness rejection. As the courts have stated, the fact that it is necessary to cite such a large number of references is, in and of itself, indicative of non-obviousness. *Minneapolis-Honeywell Regulator Company v. Midwestern Instruments, Inc.*, 298 F.2d 36, 38, 131 U.S.P.Q. 402, 403 (7th Cir. 1961); *The Ric-Wil Company v. E.B. Kaiser Company*, 179 F.2d 401, 404, 84 U.S.P.Q. 121, 124 (7th Cir. 1950); *Reynolds et al v. Whitin Machine Works*, 167 F.2d 78, 83, 76 U.S.P.Q. 551, 555 (4th Cir. 1948); and *Racial-Vadic, Inc. v. Universal Data Systems*, 1980 U.S. Dist. LEXIS 15864, *81, 207 U.S.P.Q. 902, 927 (N.D. Ala. 1980).

is entirely consistent with what BHA and PG are well known for, namely the prevention of rancidity in oils and fats (*see* section 7 of the attached extracts).

In stark contrast, in the present invention involves the use of aromatic alcohols (such as the BHA and PG) in the aqueous environment of the intestine, in order to enhance the solubility of bile salts. As explained at pages 2 and 3 of the present application as filed, this is based on the surprising discovery that certain aromatic alcohols (which normally have very low solubility in water) are able to enhance the solubility of non-conjugated bile salts at pH levels below 7. This is emphasized in claim 1 by the requirement for a bile salt to be present in combination with the aromatic alcohol. It is emphasized yet further by the newly introduced requirement that the ratio by weight of the non-conjugated bile salt + additive to the active macromolecular principle is at least 3:1.

Accordingly, both the purpose of the antioxidant compound and the environment in which they are employed in Desai are completely different to the purpose and environment of the aromatic alcohols used in the compositions of the present invention. Clearly, the optional use of antioxidants in a lipid component of a microemulsion described by Desai does not lead onto, and indeed teaches away from a composition of claim 1.

Moreover, the combination suggested by the Examiner, i.e. New ('748) and Desai (among others), is incompatible because of the teaching of New ('748). In particular, in Desai the compounds are used in a lipid phase whereas New ('748) discusses the use of its compositions in the aqueous environment of the intestines, *see* e.g. col. 3 lines 49-52.

Furthermore, there is no implication in Desai that the agents PG and/or BHA are common in formulations of insulin (or indeed other macromolecules), and so one skilled in the art would not have been inclined to include them in such a formulation on that basis. That is even more so in view of the fact that none of the Examples given in Desai include these compounds.

In fact, Desai provides evidence that teaches directly against the reasoning used by the Examiner in the Office Action, because in each of the compositions it exemplifies, a buffer is used (to adjust the pH), and the buffer is completely different from BHA and PG. Thus, Examples 1 and 4 use a citrate buffer (col. 6 lines 56-60, col. 7 lines 34-36 and col. 11 line 22), and Examples 2 and 3 a phosphate buffer.

Actually, Desai is merely one example of a vast number of prior art documents which demonstrate the use of citrate and phosphate buffers. Other buffers are of course also well known and widely used in pharmaceutical compositions. This reinforces the point that it cannot be the case that a skilled person would even consider (let alone think obvious) trying to use BHA or PG as a buffer when there is such a wealth of well known tried and tested buffers already in existence, and especially given that the use of either BHA or PG has never even been suggested.

Makino et al:

This document discusses a formulation containing vitamin D3, a small water-insoluble molecule. It is very susceptible to oxidation and PG is mentioned as a possible antioxidant additive. Thus, it serves an entirely different purpose compared to its use in the compositions of the present invention. There is no suggestion whatsoever that it could somehow improve bile salt solubility and thereby enhance absorption of a macromolecule.

Moreover, vitamin D3 is not a macromolecule. This is evident from the accompanying extract showing the IUPAC definition for the term “macromolecule”, which shows that in order to be a macromolecule a molecule must have a structure essentially comprising multiply repeated units. Vitamin D3 has a molecular mass of 384.64 g/mol and has no repeated monomeric units. Accordingly, the use of PG in the same composition as vitamin D3 does not prove that PG could just as easily be combined with a macromolecule such as insulin, which is far more delicate, e.g. because it has a complicated tertiary structure.

It should also be noted here that claim 1 requires additive (c) to account for at least 1 % by weight of the mixture. The Examiner refers to Makino *et al* to support an assertion that it would be obvious to use such a large quantity of PG. However, the fact that Makino *et al* use PG in such a quantity in what (as discussed above), is a different context to New ('748), would not make it obvious to use it in that quantity in a composition of New. Indeed, as an antioxidant (the known use for PG), it is usual to use only a very low concentration. For instance, in WO0222158 (brought to the Examiner's attention in the IDS filed on 2 April 2007) an amount of 0.0008 to 0.0009 % is preferred for the formulations in question. Accordingly, a skilled person would not have thought it obvious to use as high a concentration as 1 % or above, e.g. for fear of prejudicing the activity of the active macromolecular principle and/or the effectiveness of the composition as a whole.

Modi et al:

This document mentions that antioxidants may be added to the compositions described. Tocopherol, derteroxime mesylate, methyl paraben and ascorbic acid are mentioned as apparently preferred antioxidants. No mention at all is made of PG or BHA. This should, in fact, come as no surprise given the poor solubility of these compounds and the fact that the Examples in Modi all involve a formulation made using distilled water. Furthermore, none of Modi's Examples even feature any of the apparently preferred antioxidants. Accordingly, Modi would not have given any motivation for a skilled person to add any antioxidant to the compositions of New ('748), let alone the compounds PG or BHA, at a concentration as high as 1 % by weight of the mixture. The idea of using PG or BHA in combination with a non-conjugated bile salt wherein the ratio by weight of the salt + PG or BHA to the active macromolecular principle is even less obvious still.

The pKa of PG, and PG as a replacement of sodium bicarbonate

It is argued that it would be obvious to modify the compositions of New by replacing the sodium bicarbonate with an additive of claim 1, because the additive of claim 1 would "have an appropriate pKa for buffering a solution between pH 7.5 and 8". With respect, the applicant disagrees with this suggestion.

Sodium bicarbonate, the agent of choice in the New '748 Patent, has a pKa of 6.3. As noted by the Examiner, PG has a pKa of 8.11. The pKa scale is, of course, a logarithmic scale. Accordingly, the disassociation constant for sodium bicarbonate is over 60 times greater than that for PG. Firstly, such a large difference in the degree of dissociation between the two compounds would put a skilled person off the suggested replacement. Moreover, PG has never been described or suggested as an acidity adjuster in pharmaceutical practice.

Further, sodium bicarbonate, an inorganic compound, and the aromatic alcohol additives of claim 1 are chemically completely different. This would clearly make PG an undesirable choice to replace sodium bicarbonate.

Consider, for instance, the differences between the solubility of additives of present claim 1 compared to that of the additive sodium bicarbonate used in New ('748). This is particularly relevant because the Examiner's reasoning relies on it being obvious to use PG as a buffer, and solubility is naturally an essential property for a buffer compound.

It is well known by any person (let alone a skilled chemist) that sodium bicarbonate is highly soluble in water. PG, in stark contrast, is highly lipophilic and very water-insoluble. This derives from its chemical structure, and in particular the hydrophobic terminal propyl groups. Evidence for this may be found, for instance, in the Handbook of Pharmaceutical Excipients. A copy of the entry for PG from the second edition of this book is attached. As can be seen, PG has a solubility in water (at 20 °C) of only 1 in 1000.

Against this background it is simply not credible to suggest that a skilled person would consider using the additives defined in claim 1 in place of sodium bicarbonate used in New ('748), let alone with any expectation of retaining the activity of New's compositions.

Incidentally, it is of note that New ('748) does not mention whether the compositions it discloses could (even optionally) contain antioxidants. In particular, there is no suggestion that even a small amount of any of the additives as defined in present claim 1 could be used.

Raising the pH above 7.5 once the composition has been introduced into the intestine

At page 8 the Examiner suggests it would be a necessary property of the composition not to raise the pH above 7.5 once it has been introduced into the intestine. No reasoning is given for this. Indeed, it is difficult to foresee a valid reason for it, given that New ('748) specifically teaches to raise the pH above 7.5.

It appears this suggestion has been made simply in order to "arrive" at a composition according to claim 1, i.e. one that does not raise the pH of the intestinal fluid above 7.5. In other words, it is a mere assertion, made with the benefit of hindsight, which is of course not permitted when assessing obviousness. With respect, the applicant therefore cannot accept it.

In view of the comments above it is respectfully submitted that the claims are not obvious from the cited prior art. Favorable reconsideration is respectfully requested.

Statement of Substance of Interview [MPEP §713.04]

An interview was held on April 8, 2008 with the inventor Dr. Roger New, the undersigned, and examiners Gupta and Ha. The substance of the interview substantially as set out in detail above and in the Interview Summary as handed to the undersigned on April 8, 2008 and in the Interview Summary mailed April 21, 2008.

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Appl. No. 10/553,169
April 28, 2008

Respectfully submitted,

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**Handbook of
PHARMACEUTICAL
EXCIPIENTS**

Second Edition

Edited by
Ainley Wade and Paul J Weller

American Pharmaceutical Association
Washington

1994

The Pharmaceutical Press
London

Propyl Gallate

1. Nonproprietary Names

BP: Propyl gallate

USPNF: Propyl gallate

2. Synonyms

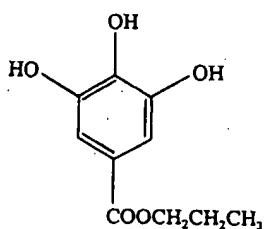
E310; gallic acid propyl ester; *Progallin P*;
n-propyl gallate; propyl 3,4,5-trihydroxybenzoate; *Tenox PG*.

3. Chemical Name and CAS Registry Number

3,4,5-Trihydroxybenzoic acid propyl ester
[121-79-9]

4. Empirical Formula Molecular Weight
C₁₀H₁₂O₅ 212.20

5. Structural Formula



6. Functional Category

Antioxidant.

7. Applications in Pharmaceutical Formulation or Technology

Propyl gallate has become widely used as an antioxidant in cosmetics, perfumes, foods and pharmaceuticals since its use in preventing autoxidation of oils was first described in 1943.^(1,2) It is primarily used, in concentrations up to 0.1% w/v, to prevent the rancidity of oils and fats; it may also be used at concentrations of 0.002% w/v to prevent peroxide formation in ether and at 0.01% w/v to prevent the oxidation of paraldehyde. Synergistic effects with other antioxidants such as butylated hydroxyanisole and butylated hydroxytoluene have been reported. Propyl gallate is also said to possess some antimicrobial properties, *see* Section 10.

Other alkyl gallates are also used as antioxidants and have approximately equivalent antioxidant properties when used in equimolar concentration; solubilities however vary, *see* Section 18.

8. Description

Propyl gallate is a white, odorless or almost odorless crystalline powder, with a bitter astringent taste which is not normally noticeable at the concentrations employed as an antioxidant.

9. Pharmacopeial Specifications

Test	BP 1993	USPNF XVII
Identification	+	+
Melting range	148-151°C	146-150°C
Loss on drying	≤ 1.0%	≤ 0.5%
Residue on ignition	—	≤ 0.1%
Sulfated ash	≤ 0.1%	—
Chloride	≤ 330 ppm	—
Sulfate	≤ 0.12%	—
Heavy metals	—	≤ 0.001%
Assay (dried basis)	—	98.0-102.0%

10. Typical Properties

Antimicrobial activity: propyl gallate has been reported to possess some antimicrobial activity against Gram-negative, Gram-positive and fungal species.⁽³⁾ Its effectiveness as a preservative may be improved when used in combination with zinc salts, such as zinc sulfate, due to synergistic effects.⁽⁴⁾ Reported minimum inhibitory concentrations (MICs) for aqueous solutions containing 4% v/v ethanol as cosolvent are shown below:⁽³⁾

Microorganism	MIC (μg/mL)
<i>Candida albicans</i>	1500
<i>Escherichia coli</i>	330
<i>Staphylococcus aureus</i>	600

Melting point: 150°C

Solubility:

Solvent	Solubility at 20°C Unless otherwise stated
Almond oil	1 in 44
Castor oil	1 in 4.5
Cottonseed oil	1 in 81 at 30°C
Ethanol (95%)	1 in 3
	1 in 0.98 at 25°C
Ether	1 in 3
	1 in 1.2 at 25°C
Lanolin	1 in 16.7 at 25°C
Lard	1 in 88 at 45°C
Mineral oil	1 in 200
Peanut oil	1 in 2000
Propylene glycol	1 in 2.5 at 25°C
Soybean oil	1 in 100 at 25°C
Water	1 in 1000
	1 in 286 at 25°C

11. Stability and Storage Conditions

Propyl gallate is unstable at high temperatures and is rapidly destroyed in oils that are used for frying purposes. The bulk material should be stored in a well-closed, nonmetallic container, protected from light, in a cool, dry, place.

12. Incompatibilities

The alkyl gallates, are incompatible with metals, e.g. sodium, potassium and iron, forming intensely colored complexes. Complex formation may be prevented, under some circumstances, by the addition of a sequestering agent, typically citric acid. Propyl gallate may also react with oxidizing materials.

13. Method of Manufacture

Propyl gallate is prepared by the esterification of 3,4,5-trihydroxybenzoic acid (gallic acid) with *n*-propanol. Other alkyl gallates are similarly prepared using an appropriate alcohol of the desired alkyl chain length.

14. Safety

It has been reported, following animal studies, that propyl gallate has a strong contact sensitization potential.⁽⁵⁾ However, despite this, there have been few reports of adverse reactions.⁽⁶⁾ Those that have been described include: contact dermatitis; allergic contact dermatitis;⁽⁷⁾ and methemoglobinemia in neonates.⁽⁸⁾

The WHO has set an estimated acceptable daily intake for propyl gallate at up to 2.5 mg/kg body-weight.⁽⁹⁾

LD₅₀ (cat, oral): 0.4 g/kg⁽¹⁰⁾

LD₅₀ (mouse, oral): 1.7 g/kg

LD₅₀ (rat, oral): 3.8 g/kg

LD₅₀ (rat, IP): 0.38 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. When heated to decomposition propyl gallate may emit toxic fumes and smoke.

16. Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IM injections and topical preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Aust, Br, Cz, Egypt, Fr, Ind, Nord and USPNF.

18. Related Substances

Dodecyl gallate; ethyl gallate; octyl gallate.

Dodecyl gallate: C₁₉H₃₀O₅

Molecular weight: 338.44

CAS number: [1166-52-5]

Synonyms: dodecyl 3,4,5-trihydroxybenzoate; E312; lauryl gallate.

Pharmacopeias: Aust, Br and Fr.

Appearance: white, odorless or almost odorless crystalline powder.

Melting point: 96-97.5°C

Solubility:

Solvent	Solubility at 20°C
Acetone	1 in 2
Chloroform	1 in 60
Ethanol (95%)	1 in 3.5
Ether	1 in 4
Methanol	1 in 1.5
Peanut oil	1 in 30
Propylene glycol	1 in 60
Water	practically insoluble

Ethyl gallate: C₉H₁₀O₅

Molecular weight: 198.17

CAS number: [831-61-8]

Synonyms: ethyl 3,4,5-trihydroxybenzoate.

Pharmacopeias: Br.

Appearance: white, odorless or almost odorless, crystalline powder.

Melting point: 151-154°C

Solubility:

Solvent	Solubility at 20°C
Ethanol (95%)	1 in 3
Ether	1 in 3
Peanut oil	practically insoluble
Water	slightly soluble

Octyl gallate: C₁₅H₂₂O₅

Molecular weight: 282.34

CAS number: [1034-01-1]

Synonyms: E311; octyl 3,4,5-trihydroxybenzoate.

Pharmacopeias: Br and Fr.

Appearance: white, odorless or almost odorless crystalline powder.

Melting point: 100-102°C

Solubility:

Solvent	Solubility at 20°C
Acetone	1 in 1
Chloroform	1 in 30
Ethanol (95%)	1 in 2.5
Ether	1 in 3
Methanol	1 in 0.7
Peanut oil	1 in 33
Propylene glycol	1 in 7
Water	practically insoluble

19. Comments

Propyl gallate has been reported to impart an 'off' flavor to corn and cottonseed oils when used as an antioxidant.⁽¹¹⁾

An acceptable daily intake for dodecyl gallate and octyl gallate was not set by the WHO due to insufficient data. The use of octyl gallate in beer and other widely consumed beverages was however not recommended by the WHO due to the possibility of adverse reactions in the buccal mucosa of individuals previously sensitized by cutaneous contact with this compound.⁽⁹⁾

20. Specific References

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21. General References

Johnson DM, Gu LC. Autoxidation and antioxidants. In: Swarbrick J, Boylan JC, editors. *Encyclopedia of pharmaceutical technology*, volume 1. New York: Marcel Dekker Inc, 1988: 415-449.

22. Authors

UK: PJ Weller.

Butylated Hydroxyanisole

1. Nonproprietary Names

BP: Butylated hydroxyanisole

USPNF: Butylated hydroxyanisole

2. Synonyms

Antrancine 12; BHA; *tert*-butyl-4-methoxyphenol; 1,1-dimethylethyl-4-methoxyphenol; E320; *Embanox BHA*; *Nipanox BHA*; *Nipantiox 1-F*; *PM 1787*; *PM 1788*; *PM 12366*; *Sustane 1-F*; *Tenox BHA*.

3. Chemical Name and CAS Registry Number

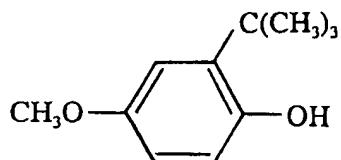
2-*tert*-Butyl-4-methoxyphenol [25013-16-5]

4. Empirical Formula Molecular Weight

C₁₁H₁₆O₂ 180.25

The BP 1993 describes butylated hydroxyanisole as 2-*tert*-butyl-4-methoxyphenol containing a variable amount of 3-*tert*-butyl-4-methoxyphenol.

5. Structural Formula



Functional Category

Antioxidant.

7. Applications in Pharmaceutical Formulation or Technology

Butylated hydroxyanisole is an antioxidant with some antimicrobial properties.⁽¹⁾ It is used in cosmetics, foods and pharmaceuticals particularly to delay or prevent oxidative rancidity of fats and oils and to prevent loss of activity of oil-soluble vitamins.

Butylated hydroxyanisole is frequently used in combination with other antioxidants, particularly butylated hydroxytoluene and alkyl gallates, and with sequestrants or synergists such as citric acid.

Antioxidant use	Concentration (%)
β-Carotene	0.01
Essential oils and flavoring agents	0.02-0.5
IM injections	0.03
IV injections	0.0002-0.0005
Oils and fats	0.02
Topical formulations	0.005-0.02
Vitamin A	10 mg per million units

8. Description

Butylated hydroxyanisole occurs as a white or almost white crystalline powder or a yellowish-white waxy solid with a faint, characteristic aromatic odor.

9. Pharmacopeial Specifications

Test	BP 1993 (Ad 1994)	USPNF XVII (Suppl 6)
Identification	+	+
Residue on ignition	—	≤ 0.01%
Sulfated ash	≤ 0.05%	—
Related substances	+	—
Arsenic	—	≤ 3 ppm
Heavy metals	—	≤ 0.001%
Organic volatile matter	—	+
Assay	—	≥ 98.5%

10. Typical Properties

Antimicrobial activity: activity is similar to that of the *p*-hydroxybenzoate esters (parabens). The greatest activity is against molds and Gram-positive bacteria, with less activity against Gram-negative bacteria.

Boiling point: 264°C

Melting point: 47°C (for pure 2-*tert*-butyl-4-methoxyphenol), *see also* Section 19.

Solubility: practically insoluble in water; freely soluble in ≥ 50% aqueous ethanol, propylene glycol, chloroform, ether, hexane, cottonseed oil, peanut oil, soybean oil and in solutions of alkali hydroxides. *See also* HPE Data.

Specific gravity: 1.05 at 20°C

Viscosity (kinematic): 3.3 mm²/s (3.3 cSt) at 99°C

HPE Laboratory Project Data			
Method	Lab #	Results	
Density	DE-1	31	1.117 g/cm ³
Solubility			
Ethanol (95%) at 25°C	SOL-7	32	793.0 mg/mL
Ethanol (95%) at 37°C	SOL-7	32	834.0 mg/mL
Hexane at 25°C	SOL-7	32	48.0 mg/mL
Hexane at 37°C	SOL-7	32	10.0 mg/mL
Propylene glycol at 25°C	SOL-7	32	467.0 mg/mL
Propylene glycol at 37°C	SOL-7	32	456.0 mg/mL
Water at 25°C	SOL-7	32	0.32 mg/mL
Water at 37°C	SOL-7	32	0.78 mg/mL

Supplier: Eastman Fine Chemicals.

11. Stability and Storage Conditions

Exposure to light causes discoloration and loss of activity. Butylated hydroxyanisole should be stored in a well-closed container, protected from light, in a cool, dry, place.

12. Incompatibilities

Butylated hydroxyanisole is phenolic and undergoes reactions characteristic of phenols. It is incompatible with oxidizing agents and ferric salts. Trace quantities of metals, and exposure to light, cause discoloration and loss of activity.

13. Method of Manufacture

Prepared by the reaction of *p*-methoxyphenol with isobutene.

14. Safety

Butylated hydroxyanisole is absorbed from the gastrointestinal tract and is metabolized and excreted in the urine with less than 1% unchanged within 24 hours of ingestion.⁽²⁾ Although there have been some isolated reports of adverse skin reactions to butylated hydroxyanisole^(3,4) it is generally regarded as nonirritant and nonsensitizing at the levels employed as an antioxidant.

Concern over the use of butylated hydroxyanisole has occurred following long-term animal feeding studies. Although previous studies in rats and mice fed butylated hydroxyanisole at several hundred times the US permitted level in the human diet showed no adverse effects, a study in which rats, hamsters and mice were fed butylated hydroxyanisole at 1-2% of the diet produced benign and malignant tumors of the forestomach, but in no other sites. However, humans do not have any region of the stomach comparable to the rodent forestomach and studies in animals that also do not have a comparable organ (dogs, monkeys and guinea pigs) showed no adverse effects. Thus, the weight of evidence does not support any relevance to the human diet where butylated hydroxyanisole is ingested at much lower levels.⁽⁵⁾ The WHO acceptable daily intake of butylated hydroxyanisole has been set at 500 µg/kg body-weight.⁽⁵⁾

LD₅₀ (mouse, oral): 2.0 g/kg⁽⁶⁾

LD₅₀ (rat, IP): 0.88 g/kg

LD₅₀ (rat, oral): 2.2 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Butylated hydroxyanisole may be irritant to the eyes, skin, and on inhalation. It should be handled in a well-ventilated environment; gloves and eye protection are recommended.

16. Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (inhalations, IM and IV injections, oral capsules and tablets, rectal, topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Br, Fr, Ind, It, Mex and USPNF.

18. Related Substances

Butylated Hydroxytoluene.

19. Comments

The commercially available material can have a wide melting point range (47-57°C) due to the presence of varying amounts of 3-*tert*-butyl-4-methoxyphenol.

Tenox brands contain 0.1% w/w citric acid as a stabilizer.

20. Specific References

1. Lamikanra A, Ogunbayo TA. A study of the antibacterial activity of butyl hydroxy anisole (BHA). *Cosmet Toilet* 1985; 100(10): 69-74.
2. El-Rashidy R, Niazi S. A new metabolite of butylated hydroxyanisole in man. *Biopharm Drug Dispos* 1983; 4: 389-396.
3. Roed-Peterson J, Hjorth N. Contact dermatitis from antioxidants: hidden sensitizers in topical medications and foods. *Br J Dermatol* 1976; 94: 233-241.
4. Juhlin L. Recurrent urticaria: clinical investigation of 330 patients. *Br J Dermatol* 1981; 104: 369-381.
5. FAO/WHO. Evaluation of certain food additives and contaminants. Thirty-third report of the joint FAO/WHO expert committee on food additives. *Tech Rep Ser Wld Hlth Org* 1989; No. 776.
6. Sweet DV, editor. *Registry of toxic effects of chemical substances*. Cincinnati: US Department of Health, 1987.

21. General References

Babich H, Borenfreund E. Cytotoxic effects of food additives and pharmaceuticals on cells in culture as determined with the neutral red assay. *J Pharm Sci* 1990; 79: 592-594.

Verhagen H. Toxicology of the food additives BHA and BHT. *Pharm Weekbl Sci* 1990; 12: 164-166.

22. Authors

USA: MJ Groves.

macromolecule (polymer molecule)

A molecule of high relative molecular mass, the structure of which essentially comprises the multiple repetition of units derived, actually or conceptually, from molecules of low relative molecular mass.

Notes:

1. In many cases, especially for synthetic polymers, a molecule can be regarded as having a high relative molecular mass if the addition or removal of one or a few of the units has a negligible effect on the molecular properties. This statement fails in the case of certain macromolecules for which the properties may be critically dependent on fine details of the molecular structure.
2. If a part or the whole of the molecule has a high relative molecular mass and essentially comprises the multiple repetition of units derived, actually or conceptually, from molecules of low relative molecular mass, it may be described as either macromolecular or polymeric, or by polymer used adjectively.

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